

COCAINE USE DURING PREGNANCY: MATERNAL DEPRESSIVE SYMPTOMS
AND INFANT NEUROBEHAVIOR OVER THE FIRST MONTH

BY

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TABLE OF CONTENTS

	page
ACKNOWLEDGEMENTS.....	ii
ABSTRACT.....	v
CHAPTERS	
I INTRODUCTION.....	1
Overview of Teratology.....	3
Developmental Toxicity: Licit Drugs.....	5
Alcohol.....	5
Tobacco.....	8
Caffeine.....	10
Developmental Toxicity: Illicit Drugs.....	12
Heroin/Methadone.....	12
Marijuana.....	14
Cocaine.....	15
Maternal Depression.....	27
Research Goals.....	31
II METHODS.....	34
Subjects.....	34
Measures.....	36
Brazelton Neonatal Behavioral	
Assessment Scale.....	36
Beck Depression Inventory.....	42
Procedures.....	42
III RESULTS.....	46
IV DISCUSSION.....	66
Continuum of Casualty.....	67
Future Research.....	67
APPENDIX.....	71
REFERENCES.....	74
BIOGRAPHICAL SKETCH.....	92

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The dramatic increase in the number of infants identified as prenatally cocaine-exposed has spurred public and scientific debate about the potential adverse effects on the fetus, neonate and child. Research to date has failed to establish a consistent pattern of results; even studies conducted at the same research center have yielded different findings. These inconsistent outcomes may be due in part to differences in research design and procedures. Previous studies have been confounded by sample differences that place the groups at risk for poor outcome independent of cocaine exposure. In addition, it is not clear that examiners were completely blinded to the drug exposure status of the infants.

The goals of this project were: 1) to improve upon the methodology used in previous research by concurrently testing exposed and non-exposed infants to avoid examiner

bias and matching subjects one-to-one on important confounding maternal and infant variables, 2) to assess the impact of prenatal cocaine exposure on the previously unstudied population of neonates born to women receiving little or no prenatal care or drug treatment, 3) to investigate the unknown impact of cocaine use during pregnancy on maternal depressive symptoms both immediately and one month postpartum, 4) to investigate the potential impact of increased maternal depressive symptoms on subsequent infant neurobehavior, and 5) to provide the first longitudinal data regarding the neurobehavioral development of cocaine-exposed neonates by assessing the infants in the hospital and at one month of age with the Brazelton Neonatal Behavioral Assessment Scale (BNBAS).

Thirty-five cocaine-exposed mother-infant dyads and 35 non-exposed dyads were assessed following delivery. Groups were matched one-to-one on the following variables: maternal race, tobacco use, primi- or multiparity, weight for gestation, and type of delivery. Cocaine-using mothers had significantly fewer prenatal visits and lower scores on the Beck Depression Inventory immediately following delivery. Cocaine-exposed infants had significantly lower birthweights and shorter gestations than did matched controls. There were no significant differences between the groups on the BNBAS after birth or at one month of age.

CHAPTER I

INTRODUCTION

Research during the infant period offers a unique opportunity to examine the relationship between biology and environment. While the prenatal environment can be important and biological influences do continue throughout the lifespan, there is no other developmental stage when their influences can be as clearly separated.

Currently there is a great deal of interest in the effects of prenatal cocaine-exposure on infants. Politicians, scientists, and the public appear to view these babies as the most devastating manifestation of this country's drug problem. Certainly, the image of babies as innocent victims is horrible. However, as researchers it is our responsibility to study this situation in an unbiased manner and to rationally determine the impact of this unfortunate maternal behavior.

In the case of prenatal drug exposure neonatal research is extremely important. If we do not begin by establishing the existence of direct or indirect

effects in the neonatal period, then behavioral or physical abnormalities observed later can never clearly be attributed to exposure during gestation. Poor developmental outcome in childhood could be the result of prenatal exposure, dysfunctional caregiving, and/or a self-fulfilling prophecy of low expectations for normal development. Only through longitudinal research will we be able to understand the separate and combined effects of these potential influences.

In addition, the behavioral effects of prenatal substance exposure may be easier to detect in the neonatal period. Research indicates that the severity of outcome is influenced by the time since damage, therefore the earlier testing occurs the more likely it is that behavioral effects will be detected. Furthermore, the long-term effects of brain damage are typically not as severe as those noted soon after the injury (Amlil & Finger, 1984; Finger & Amlil, 1984; Finger & Stein, 1982). If such plasticity is operating, then a meaningful amount of recovery may be possible following damage due to teratogenic or toxic exposure during gestation. However, even transient behavioral dysfunctions during the neonatal period could alter later development by changing the interaction between infant and parent (Riley, Hannigan, & Balaz-Hannigan, 1985).

Overview of Teratology

The implicit goal of research on cocaine-exposed infants is to determine the teratogenic effects of cocaine. The thalidomide tragedy of the late fifties and early sixties opened the eyes of the world to the potentially devastating effects of substances consumed by pregnant women. Prior to that time, the study of the adverse effects of environmental substances on the developing fetus was the domain of a small group of teratologists. Following the thalidomide tragedy a wave of new investigators were drawn to the field. These biomedical, neuroscience, and psychological researchers were attracted by the implications of teratological phenomena. It had become clear that exposure of the embryo and fetus to external chemicals could alter both structural and functional development. This expanded scope produced a new research specialty called behavioral teratology.

Recently in an effort to increase precision and specificity, new terminology has evolved. For example, many researchers now agree that the term "teratogen" should be used only to denote conditions or compounds that produce dysmorphogenesis (i.e., gross structural malformations). The broader term "developmental toxin" includes all adverse chemical effects on the normal

sequence of development, including behavioral alterations. These less ambiguous definitions facilitate communication and specificity. For example, both alcohol and opiates are developmentally toxic; however, alcohol is a teratogen because it can produce congenital anomalies, while the toxic effects of opiates are expressed primarily as central nervous system (CNS) dysfunction (Hutchings, 1987).

The following review of developmentally toxic effects of various drugs of abuse will focus on human research and emphasize the impact on neurobehavior. Both licit and illicit, central nervous system stimulants and depressants will be reviewed. Legality is an important issue in prenatal exposure research. Illegal drugs are more difficult to study due to issues such as maintenance of confidentiality, possibly criminal lifestyles of subjects, and increased likelihood of polydrug use. In addition, it is difficult to establish the quantity and quality of drugs used illegally. Chemical adulterants are often added to illegal drugs in order to increase profit.

Stimulants and depressants can impact both the user and the CNS in different ways. There is no reason to expect the developmentally toxic effects to follow similar patterns of physical or behavioral effects. Due to the likelihood of polydrug use it is important

to acknowledge and understand the effects of these different drugs of abuse on the fetus in order to clarify the separate, antagonistic, or synergistic influence of prenatal cocaine exposure on fetal or infant development.

Developmental Toxicology: Licit Drugs

Alcohol

Alcohol is now recognized as the leading known teratogen in the world (Abel & Sokol, 1987; Schardein, 1985). In sufficient quantities alcohol, a CNS depressant, produces Fetal Alcohol Syndrome (FAS). This syndrome is characterized by a stereotyped pattern of malformation, growth deficiency, and CNS dysfunction which is reflected in mental and psychomotor deficiencies of varying degrees (Clarren & Smith, 1978; Jones & Smith, 1973). Fetal Alcohol Syndrome children have been shown to exhibit withdrawal, learning difficulties, low scores on tests of intelligence, hyperactivity, altered muscle tone, lack of fine and gross motor coordination, and mental retardation (Colangelo & Jones, 1982; Shaywitz, Cohen, & Shaywitz, 1980; Striessguth, Herman, & Smith, 1978; Streissguth, Landesman-Dwyer, Martin, & Smith, 1980). Recent reports estimated the incidence of FAS in the United

States at about 2.2 per thousand live births (Abel & Sokol, 1987).

Even in the absence of FAS, heavy prenatal alcohol-exposure has been related to higher rates of low birth weight (Ouellette, Rosett, Rosman, & Weiner, 1977; Sokol, Miller, & Reed, 1980), spontaneous abortion (Berkowitz, 1981; Harlap & Shiono, 1980; Kline, Shrout, Stien, Susser, & Warburton, 1980), and an increased incidence of malformations (Ouellette et al., 1977; Rosett et al., 1983; Streissguth, Martin, Martin, & Barr, 1981). Some studies, however, have reported no relationship between level of maternal alcohol consumption and lower birth weight (Hingson et al., 1982; Tennes & Blackard, 1980;), prematurity (Hingson et al., 1982; Little, Streissguth, Barr, & Herman, 1980; Sokol et al., 1980; Tennes & Blackard, 1980), or likelihood of congenital abnormality (Flynn et al., 1981; Tennes & Blackard, 1980). Rosett et al. (1983) and Olegard et al. (1979) have both found that abstinence during the latter part of the pregnancy reduced the incidence of growth retardation but not congenital anomalies.

Prenatal alcohol-exposure has been found to produce neurobehavioral effects on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS; Brazelton, 1984). Researchers have found slower habituation

(Streissguth, Barr, & Martin, 1983), lower scores on range of state (Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984), and negative alterations in reflexes, activity level, and motor behavior (Coles, Smith, Fernhoff, & Falek, 1985). In contrast, Ernhart et al. (1985) found no relationship between BNBAS performance and prenatal alcohol exposure when marijuana and tobacco use were controlled. Richardson, Day, & Taylor (1989) reported a relationship between moderate alcohol consumption during the first and second trimester and BNBAS orientation behavior; however, they emphasized that alcohol use accounted for only 1% of the variance. In fact, the most consistent predictor of BNBAS performance in their study was the variable of the different examiners who administered the BNBAS.

Researchers (Smith, Coles, Lancaster, Fernhoff, & Falek, 1986) studying the effects of alcohol use during pregnancy have found that infants exposed to heavy use of alcohol (average of 12 ounces absolute alcohol/week) at any time during pregnancy were found to have more abnormal reflexes, less mature motor behavior, and increased activity levels than those who had no instance of heavy alcohol use. Infants of mothers who continued to drink throughout pregnancy were significantly poorer in orientation, motor performance, and autonomic regulation than were infants of mothers

who stopped drinking. At one month follow-up infants in the stopped-drinking group showed more recovery than the continued-drinking group in reflexive behavior and autonomic control.

Tobacco

Tobacco is a central nervous system stimulant and is probably the most common addictive substance used by pregnant women. Only about 20% of smokers who become pregnant quit during pregnancy (Prager, Malin, Spiegler, Vanatta, & Placek, 1984). Lower birthweight is the most consistently reported result of maternal smoking (Abel, 1980; Cnattiguais, Axelsson, Elkund, & Lindmark, 1985; Kline, Stein, & Hutzler, 1987). The reduction in birthweight has averaged about 170-200 grams (Meredith, 1975). A significant dose-response relationship has been found, including normal birthweight at term when mothers stop smoking early in pregnancy (Murphy & Mulcahy, 1971). Using ultrasound, researchers have compared growth curves of biparietal diameters (BPD) for fetuses of smokers and nonsmokers throughout pregnancy. The BDP increased faster for fetuses of nonsmokers and decreased growth was correlated with average number of cigarettes smoked (Murphy, Drumm, Mulcahy, & Daily, 1980; Persson, Grennert, Gennser, & Kullander, 1978).

The risk of preterm delivery appears to be moderately increased for women who smoke and is related to the level of maternal smoking (Berkowitz, Holford, & Berkowitz, 1982; Shiono, Klebanoff, & Rhoads, 1986). There is a higher incidence of abruptio placentae, placenta previa, vaginal bleeding, and probably premature rupture of membranes (Meyer, Jonas, & Tonascia, 1976; Meyer & Tonascia, 1977; Naeye, 1978; 1980). Longo (1982) considers smoking to be the single most important and preventable determinant of low birthweight and perinatal mortality in the United States.

Interestingly, smokers have been found to have a lower incidence of preeclampsia and toxemia. It has been hypothesized that this lower rate is due to the hypotensive effects of tobacco use (Andrews, 1973; Pirani & MacGillivray, 1978). However, when preeclampsia does develop, the rate of perinatal mortality has been found to be higher (Andrews & McGarry, 1972; Butler & Alberman, 1962).

Long-term effects on infants of maternal smoking are difficult to evaluate due to the confounding factor of chronic passive exposure following birth. For that reason those studies will not be reviewed.

It should be remembered that tobacco contains over 2000 different compounds, including carbon monoxide,

nicotine, cyanide, and cadmium, and it has not been possible to determine the contributions of each of these different compounds. Currently the most widely accepted explanation for the detrimental effects of smoking on the fetus and newborn is that smoking causes an increase in catecholamine levels which produces vasoconstriction and reduced blood flow to the placenta, resulting in intrauterine hypoxia (Abel, 1980; Andrews & McGarry, 1972; Longo, 1977).

Neurobehavioral differences in the neonatal period related to prenatal tobacco-exposure have included poorer auditory orientation, autonomic regulation (e.g., more tremors and startles) and faster auditory habituation (Piccone, Allen, Olsen, & Ferris, 1982). Other studies have found no effect of tobacco use on neurobehavioral performance (Richardson, Day, & Taylor, 1989; Tennes et al., 1985).

Caffeine

Caffeine is included in several popular beverages and is a component in a substantial portion of prescription and over-the-counter medications. Animal teratology studies demonstrate quite convincingly that caffeine is teratogenic in laboratory animals (e.g., Collins, Welsh, Black, & Collins, 1981). Levels involved in human consumption, however, do not appear

to be dangerous. Following initial retrospective reports of congenital anomalies related to prenatal caffeine exposure (Borlee, Lechat, Bouckaert, & Misson, 1978; Fredrick, 1974; Hogue, 1981), research on thousands of women has found virtually no association between prenatal caffeine exposure and birth defects (Heinone, Slone, & Shapiro, 1977; Linn et al, 1982; Rosenberg, Mitchell, Shapiro, & Slone, 1982).

Lack of human teratogenicity due to caffeine exposure does not rule out developmental toxicity. In a study focused on the teratogenic effects of alcohol, Streissguth and colleagues found a relationship between caffeine, poorer motor maturity, and lower activity levels on the BNBAS when alcohol and smoking were held constant (Streissguth, Herman, & Smith, 1978). In another study caffeine use prior to pregnancy was found to predict poorer orientation on the BNBAS and more general irritability, while use during pregnancy was related to more abnormal reflexes (Jacobson et al., 1984). On the other hand, Hronsky & Emory (1987) found no relationship between prenatal caffeine exposure and BNBAS cluster scores.

Developmental Toxicology: Illicit Drugs

Heroin/Methadone

Researchers investigating the effects of heroin or methadone initially reported that prenatal heroin exposure was associated with a high incidence of low birthweight, and perinatal mortality and morbidity (Kaltenbach & Finnegan, 1984). They also documented that methadone-maintenance and adequate prenatal care significantly reduced the incidence of these problems (Chasnoff, Hatcher, & Burns, 1982; Kandall et al., 1977). Subsequently, research on the outcome of infants prenatally exposed to methadone has yielded inconsistent results. Some studies have found lower birthweights than comparison infants (Chasnoff et al., 1982; Lifshitz, Wilson, Smith, & Desmond, 1983), while other studies have found no differences in birthweight (Rosen & Johnson, 1982; Strauss, Starr, Ostrea, Chavez, & Stryker, 1976). There have been no studies that clearly indicate an increased incidence of congenital anomalies (Ostrea & Chavez, 1979; Schardein, 1985).

Researchers have also investigated the neurobehavioral development of methadone-exposed infants. Chasnoff et al. (1982) found that methadone-exposed infants performed more poorly on several BNBAS

items including visual and auditory orientation, motor maturity, consolability, and state lability. Strauss et al. (1976) compared 25 methadone-exposed infants to controls and found no differences in Bayley Scales of Infant Development (BSID) scores at 3 and 6 months of age. However, for the methadone-exposed infants Psychomotor Development Index (PDI) scores decreased with age and were significantly different from controls at 12 months of age.

Wilson, Desmond, and Wait (1981) found no difference in Mental Development Index (MDI) scores at 9 months but did find lower PDI scores. Rosen and Johnson (1982) found no differences between groups at 6 months of age, but at 12 and 18 months of age methadone-exposed infants had both lower MDI and PDI scores. Hans and Jeremy (1984) found no differences at 4, 8, and 12 months of age; and Kaltenbach and Finnegan (1986) found no differences at 6, 12, and 24 months of age.

Kaltenbach and Finnegan (1987) compared 141 methadone-exposed infants with 127 non-drug-exposed infants matched for race, maternal age, and socioeconomic status. Methadone-exposed infants had lower birthweights and smaller head circumferences than control infants. At 6 months of age there was no

difference in mean MDI scores between the methadone-exposed and control infants.

It is important to note that, regardless of the group differences found in these studies, the MDI and PDI scores for methadone-exposed infants were all well within the range of normal development (Bayley, 1969). Also of interest is that two of the three studies that found no differences at all were presented at conferences but not subsequently published. It is widely believed that reports of negative findings are less likely to be published than those that find differences (Begg & Berlin, 1988; Rosenthal, 1979), and some data suggest this belief may be accurate (Dickerson, Chan, Chalmers, Sacks, & Smith, 1986; Koren, Graham, Shear, & Einarson, 1989; Simes, 1986).

Marijuana

The evidence regarding prenatal marijuana exposure and its effect on birthweight is sparse and conflicting. Some researchers report lower birthweights (Hingson et al., 1982), some find no association (Fried, 1982; Linn et al., 1983), and Kline et al. (1987) found no association in the first phase of their study and lower birthweights in a similar, second phase.

Marijuana use during pregnancy has been related to mild withdrawal symptoms (Fried, Watkinson, Dillon, & Dulberg, 1987). Infants who were exposed to more than five marijuana cigarettes a week throughout pregnancy exhibited increased tremors and startles and altered visual responsiveness on the BNBAS (Fried, 1980; Fried, 1982; Fried & Makin, 1987). These symptoms had attenuated by 30 days and no developmental impairments were observed at one year of age (Fried, 1982). Two other studies using the BNBAS found no relationship between marijuana use and neonatal neurobehavior (Richardson et al., 1989; Tennes et al., 1985).

Cocaine

Cocaine, a powerful short-acting psychomotor stimulant, has become the illicit drug of choice for millions of drug-using Americans, including pregnant women (Johnson, O'Malley, & Bagehman, 1985). There are conflicting reports of cocaine's teratogenicity in animal studies. Some researchers have reported congenital anomalies as a result of cocaine administration during gestation (Mahalik, Gautieri, & Mann, 1980); while other researchers have observed no signs of teratogenicity (Fantel & Macphail, 1982; Giordano et al., 1990). Studies on the teratogenicity of cocaine in humans have also produced conflicting

results, with some researchers reporting no effects (Hadeed & Siegel, 1989; Madden, Payne, & Miller, 1986) and others describing observations of urogenital malformations (Chasnoff, Burns, Scholl, & Burns, 1985; Chasnoff, Chisum, & Kaplan, 1988; Ryan, Ehrlich, & Finnigan, 1987) or only urinary tract defects (Chavez, Mulinare, & Cordero, 1989).

Because cocaine is a potent CNS stimulant, some researchers have looked for possible effects on the development of motor ability in animals. Hutchings, Fico, and Dow-Edwards (1989) found heightened activity on postnatal days 20 and 23 in rats exposed to 60 mg/kg cocaine during gestation but not in those exposed to 30 mg/kg cocaine hydrochloride. From gestational days 8 to 22 rats had received daily administration of cocaine dissolved in sterile water by gastric intubation. Spear et al. (1989) injected rats with 40 mg/kg cocaine daily from gestational days 8 to 12. They found no differences in pregnancy parameters but did observe significant deficits in learning of an odor/milk association, an increase in locomotor activity and attenuated wall climbing precipitated by footshock, despite the absence of any alteration in footshock sensitivity. Smith, Mattran, Kurkjian, and Kurtz (1989) found that chronic administration of a modest dose of cocaine (10 mg/kg from gestation days 4 to 18)

altered a number of behaviors in the offspring, including the development of open field activity, water maze performance, and footshock sensitivity. In contrast to these reports, Giordano et al. (1990) found no effect of cocaine administration (30 mg/kg from gestation days 12 to 21) on any physical or behavioral measures either following birth or at sixty days postnatally.

Research on the developmental toxicity of cocaine in humans has not revealed a consistent pattern of effects. Using mostly retrospective study designs, researchers have reported a diverse and variable set of findings including lower gestational age, reduced birth weight, reduced length or head circumference, increased incidence of intrauterine growth retardation, lower Apgar scores, and higher rates of sudden infant death syndrome. Reported obstetrical problems have included higher rates of abruptio placentae, spontaneous abortion, premature rupture of membranes, and stillbirth (Bingol, Fuchs, Diaz, Stone, & Gromisch, 1987; Frank et al., 1988; Hadeed & Siegel, 1989; Kaye, Elkind, Goldberg, & Tytun, 1989; MacGregor, Keith, Bachicha, & Chasnoff, 1989; MacGregor, et al., 1987; Neerhof, MacGregor, Retsky, & Sullivan, 1989; Ryan, Ehrlich, & Finnegan, 1987; Zuckerman et al, 1989).

All of the published data using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) to assess the neurobehavioral development of cocaine-exposed infants have come from studies by Ira Chasnoff and his colleagues. They have conducted two basic studies, (Chasnoff, Burns, Schnoll, & Burns, 1985; Chasnoff, Griffith, MacGregor, Dirkes, & Burns, 1989) portions of which have been reported in several different sources (Chasnoff, 1989; Chasnoff, Burns, & Burns, 1987; Chasnoff & Griffith, 1989; Chasnoff, 1989; Chasnoff, Lewis, Griffith, & Willey, 1989). For the purpose of simplicity, the two most complete versions will be described here.

In 1985, Chasnoff, Burns, Scholl, and Burns published the first study on the neurobehavioral performance of cocaine-exposed neonates. The women in their study were participants in a prenatal intervention program which provided intensive drug treatment and obstetrical care to pregnant substance abusers who voluntarily enrolled prior to the 12th week of pregnancy. Pregnant women with an addiction to heroin are placed on a methadone maintenance for the duration of their pregnancies. There were four groups in the study. Women who used both cocaine and methadone during pregnancy (n=11), women who only used cocaine (n=12), women who used only methadone (n=15),

and a control group with no history of cocaine or heroin use ($n=15$).

It is difficult to interpret the results reported in this study for two reasons. First of all, a large number of statistical comparisons were conducted. Secondly, the findings described in the abstract and discussion sections are not consistent with those reported in the results section.

Statistical analyses for the neurobehavioral data included the following: an analysis of variance comparing the four infant groups on the 47 individual behavioral and reflex BNBAS items, as well as an analysis of variance to compare mean differences for four a priori clusters (Als, 1978) for the four groups of infants. Finally, additional and apparently redundant chi-square analyses were conducted between the groups on the degree of tremulousness and number of startle responses. The number of statistical comparisons conducted exceeded the number of subjects in the study ($N=53$). In addition, there is no indication that the authors corrected for the inflation of the alpha level that would result from these repeated comparisons.

In both the abstract and discussion, it was reported that infants exposed to cocaine had significant depression of interactive behavior and poor

state organization compared to the methadone or control groups. In the results section however, it was reported that, "Multiple internal comparisons revealed that infants exposed to methadone had significantly worse scores in the interactive cluster than did control infants" (p. 668). This finding was also presented in a table where the mean for the methadone group is larger than those for the other groups (large cluster scores indicate less optimal performance). In addition, the table clearly indicated that the methadone group was significantly different from the control group on the interactive cluster, while the only significant difference listed for the cocaine group was on the state organization cluster. Based on the data reported in the results section it appears that the infants exposed only to cocaine during pregnancy exhibited less optimal state organization in this study than did the methadone and control infants, while it was the methadone infants who exhibited depressed interactive abilities.

In any discussion of the effects of prenatal cocaine-exposure, whether occurring in the media, scientific journals, or at professional conferences, one of the most commonly stated characteristics of these infants is that they tremor and startle more than normal infants, a symptom generally associated with

withdrawal from narcotic drugs such as heroin. Review of the literature, however, reveals that the only report of this finding with cocaine-exposed infants is the 1985 article by Chasnoff and colleagues.

Unfortunately, it is possible that this was a spurious finding due to the number of statistical comparisons.

In this study cocaine-exposed infants reportedly exhibited more tremors and startles based upon chi-square analysis but not on analysis of variance of the BNBAS individual items. In addition, no differences were found among the groups on the physiological cluster which is comprised of only three individual items (tremors, startles, and skin color).

This issue of jitteriness is important since many physicians consider increased tremors or startles to be a potential indicator of maternal cocaine use and therefore order urine screens to test for cocaine metabolites based on this symptomatology.

Interestingly, in a recent study conducted in Boston it was determined that 44% of 936 healthy fullterm neonates exhibited jitteriness during a 10 minute neurological assessment. Marijuana was used by 25% of the women and 15% used cocaine. Infants who had been exposed prenatally to marijuana, but not cocaine, were the ones found to be more likely to jitter (Parker et al., 1990). Furthermore, at our own institution we

have found that drug screening based on maternal or infant perinatal risk factors is not effective at accurately identifying prenatal cocaine users (Behnke, Eyler, Conlon, Adams, & Stewart, 1990).

In their second study, Chasnoff, Griffith, MacGregor, Dirkes, and Burns (1989) used the BNBAS to compare infants who were exposed to cocaine only during the first trimester, infants exposed throughout gestation, and drug-free infants who as a group did not statistically differ from the cocaine groups on the variables maternal age, SES, and amount of tobacco use. Both cocaine-exposed groups showed significantly lower mean cluster scores (Lester, 1984) in the areas of orientation, motor performance, state regulation, and number of abnormal reflexes. In fact, all of the drug-free infants achieved an awake and alert state during the exam while only 66% of the infants with first trimester exposure and 78% of the those exposed throughout pregnancy were able to achieve an alert state.

Interestingly, the infants exposed to cocaine throughout pregnancy performed significantly better on the range of state cluster. This cluster assesses the amount of stimulation tolerated before the infant cries, the quality of the infant's crying, the amount of irritable fussing, and the frequency of state

changes. Excessive crying and fussiness are often reported in the media as being characteristics of "cocaine babies".

Of particular note is the failure to find group differences on the autonomic regulation cluster which assesses skin color and the number of tremors and startles. This is consistent with the argument that Chasnoff's earlier report of increased tremors and startles may in fact have been a spurious finding.

The findings described in these studies raise concerns about the interactive abilities, state organization, and motoric development of cocaine-exposed infants; however, there are a few methodological problems in the Chasnoff et al. studies that may have affected the results. The first study described (Chasnoff et al., 1985) had small sample sizes, extensive statistical analyses, and no matching for potentially confounding variables, such as, maternal race, smoking, alcohol use, or parity. The second study (Chasnoff, Griffith, et al., 1989) also did not match one-to-one for these variables and, in fact, reported no alcohol or marijuana use in the control group but use by women in both cocaine groups. An additional problem in that study was that 20% of the infants whose mothers used cocaine throughout pregnancy were born small for gestational age. While this may in

fact have been an outcome of maternal cocaine use, there are other causes of growth retardation including maternal smoking or alcohol use. For this reason it is difficult to interpret whether the behavioral differences between the groups are a result of cocaine-exposure or size indirectly affected by cocaine, alcohol and/or tobacco use. If control and cocaine-exposed samples are matched for size appropriateness or for other factors likely to be associated with intrauterine growth retardation, then any differences in neonatal neurobehavior can be attributed more clearly to maternal cocaine use.

Another problem with the 1989 study is that it is not clear exactly how and when the control groups were selected and tested. Data from the cocaine-exposed groups but not the control group were presented at an earlier conference. If in fact the groups were not tested concurrently, examiners were likely to have developed suspicions concerning which group of infants were currently being tested. Even if blind to infant status, testers may have come to expect and exaggerate any real group differences.

Because the BNBAS is designed to assess the interactive abilities of infants, the examiner must have flexibility in how and when to present the various items. This flexibility combined with a 9-choice

scoring system may result in opportunities for unconscious biases to skew results. For example, Brazelton (1984) encourages evaluators who assess premature infants to continue testing fullterm infants to avoid any drift or change in their administration or scoring of the BNBAS.

It is important to remember that women who use drugs during pregnancy are likely to have many other risk factors for poor infant outcome. Supporting information has come from longitudinal studies of methadone-maintained women. Fiks, Johnson, and Rosen (1985) concluded that compared to matched drug-free controls, "methadone mothers require more assistance in parenting, are more socially isolated, and are less likely to pursue vocational and educational activities". Regan, Ehrlich, and Finnegan (1987) reported that

In addition to the chaotic lifestyle and physical discomforts of addiction which inevitably place the drug dependent women at high-risk for parenting problems, they must also cope with numerous financial, social and psychological difficulties. These include single parenthood, poor housing, inadequate income, lack of education and emotional problems. A history of having been physically and/or sexually abused during childhood is not uncommon among this group of women. (p. 315)

Research at our institution has found that cocaine users, identified through self-report and/or anonymous

urine screening, are significantly more likely to be black, single, older, multiparous and have had significantly fewer prenatal visits than the general high-risk population delivering at our hospital. They have been found to have a higher incidence of previous stillbirths, more associated chronic disease, and greater use of alcohol, cigarettes, and marijuana (Eyler et al., 1990) than matched control mothers who delivered in the same two-year period.

Follow-up of cocaine-users and their infants has been complicated by the mobility of the population, lack of transportation, the size of the region served by the hospital, and maternal fear that we are associated with the child abuse authorities. Successful follow-up has required intensive efforts including repeated contacts, incentives, and arrangement of times and locations convenient to the mothers (Eyler, Behnke, & Stewart, 1989).

MacGregor, Keith, Bachicha, & Chasnoff (1989) compared infant outcomes for cocaine-abusing women enrolled in a comprehensive prenatal care/drug treatment program and cocaine-abusing women receiving no drug treatment and little or no prenatal care but delivering at the same hospital. They found that while both groups had lower mean gestational ages, lower birthweights, and a higher incidence of preterm

delivery than did the control group; infants of cocaine-abusing women who received little prenatal care had significantly more problems on these same parameters.

In summary, current research on the neonatal neurobehavior of cocaine-exposed infants suggests that shortly following delivery neonates may exhibit more abnormal reflexes and less optimal orientation, motor, and state regulation abilities. Research to date has been conducted solely on a population of women receiving intensive drug treatment and prenatal care. Possibly confounding factors, such as, maternal tobacco use, alcohol use, parity, race, and infant size appropriateness have not been controlled. Currently there are no reports in the literature on the neurobehavioral performance of cocaine-exposed neonates beyond the first few days following delivery. In addition, there are no published data on maternal factors that might affect caregiving quality.

Maternal Depression

A number of studies have found a relationship between drug use and depression (Keeler, Taylor, & Miller, 1979; Ross & Berzins, 1974; Weissman & Myers, 1980). It is not, however, clear whether depression promotes drug use or drug use results in depression.

A study was presented at a recent conference that investigated the potential effect of maternal psychological dysfunction on the neurobehavior of cocaine-exposed infants. Griffith, Chasnoff, and Freier (1989) studied cocaine-exposed mother-infant dyads and reported that high maternal depression scores on the Minnesota Multiphasic Personality Inventory (MMPI) were related to poorer BNBAS orientation abilities of their neonates following delivery. They also found that maternal paranoia scores and total MMPI scores were related to poorer infant orientation abilities at one month.

Other research has indicated that children of depressed mothers are at high-risk for behavioral and emotional problems (Ghodsian, Zajiek, & Wolkind, 1984; Zahn-Waxler, Cummings, McKnew, & Radke-Yarrow, 1984; Zuckerman & Beardslee, 1987). Children raised by depressed mothers are two to three times as likely to suffer from depression (Weissman & Boyd, 1985). Depressed mothers have been described as more hostile and irritable toward their children (Rutter, 1966), and less affectionate and involved with their children (Weissman, Paykel, & Klerman, 1972). There is evidence that depressed mothers express flat affect during interaction with their infants, provide less stimulation, and fail to modify their behavior

according to the behavior of their infant (Cohn, Matias, Tronick, Connell, & Lyons-Ruth, 1986; Field, 1984; Field, et al., 1985). Infants as young as 3 months old whose mothers are depressed have been found to exhibit "depressed" behavior (e.g., less positive affect and lower activity level) even when interacting with a nondepressed adult (Field, et al., 1988). This suggests that they have developed a well-established defensive style of interacting regardless of the stimulation provided.

Cohn and colleagues (Cohn, Campbell, Matias, & Hopkins, 1990) have emphasized that during the postpartum period there is a relatively poor correspondence between self-reported depressive symptoms and a clinical diagnosis of depression (Hopkins, Campbell, & Marcus, 1987; O'Hara, Neunaber, & Zekoski, 1984). However, whether postpartum depression and clinical depression are manifestations of the same underlying problem, the effects on infant development and interactional styles have been documented (Zuckerman & Beardslee, 1987). In fact, Cohn and Tronick (1983) found that even brief experience with simulated maternal depression at 3 months resulted in continued negative infant affect even after the mother returned to normal interaction.

The finding that people with affective disorders are overrepresented among those undergoing inpatient or outpatient treatment for cocaine abuse suggests that mood disorders may increase susceptibility to stimulant abuse (Gawin & Kleber, 1986; Weiss, Mirin, Michael, & Sollogub, 1986). Gawin and Ellinwood (1988) have hypothesized that long-term stimulant abuse leads to sustained neurophysiological changes in brain systems that regulate psychological processes, particularly, mood states and the experience of pleasure. They feel that the persistent activation of reward pathways that results from excessive stimulant use reduces neurotransmission in the dopaminergic neurons that regulate reward. This results in the depression and inability to feel pleasure that is experienced by cocaine abusers during withdrawal.

It is possible that catecholamine levels are altered in both depression unrelated to drug use and depression that results from stimulant withdrawal. This may mean that cocaine is initially more rewarding to those suffering from depression, which leads to a greater likelihood of cocaine addiction and in turn results in even higher levels of depression when use is discontinued. Several researchers have reported that tricyclic antidepressants increase the percentage of patients who achieve abstinence (Giannini, Malone,

Giannini, Price, & Loiselle, 1986), even when subjects who met diagnostic criteria for clinical depression were excluded from the analysis (Gawin, 1986; Gawin & Kleber, 1984).

In summary, research has indicated that children and even infants of depressed parents are at high risk for behavioral and emotional problems. In addition, substance abusers and in particular cocaine abusers may be at increased risk of depressive disorders. It is possible that pregnant cocaine-users may feel more depressed because they are simultaneously dealing with the depressive cycle of cocaine use and the hormonal upheaval of pregnancy and delivery. Currently there is no published information on the levels of depression experienced by cocaine-using mothers.

Research Goals

The purpose of this study is to collect data to determine the relationships between maternal cocaine use during pregnancy, maternal depressive symptoms, and neonatal neurobehavioral development over the first month. Repeating all measures at one month after birth provides the opportunity to examine the effects of prenatal cocaine-exposure and maternal depressive affect. That is, differences in infant neurobehavior immediately following delivery would most likely be the

result of intrauterine exposure, while differences at one month could be the result of intrauterine exposure and/or maternal caregiving environment.

This study is the first to investigate the neurobehavioral development of infants born to a population of cocaine-using pregnant women who are not receiving drug treatment or intensive prenatal care. Because this population represents the majority of pregnant cocaine users it is important to determine the synergistic effects of uncontrolled cocaine use and poor prenatal health care.

Methodological improvements over the previous two studies on the neurobehavioral effects of prenatal cocaine-exposure include: a) strict procedures for maintaining examiner blindness, b) concurrent testing of cocaine- and non-exposed infants, c) samples matched one-to-one on possible confounding variables, d) inclusion of a maternal measure assessing depressive symptoms shortly after birth and one month later, e) BNBAS assessment both shortly after birth and at one month to provide longitudinal information about neurobehavioral development, and f) the opportunity to observe any effect of maternal affect on infant neurobehavior at one month of age.

Hypotheses are that prenatal cocaine exposure will lead to poorer performance on the BNBAS, most probably

in the areas of orientation, motor behavior, and state regulation. If no differences in infant neurobehavior are found following delivery, it is hypothesized that greater self-report of depressive symptoms among cocaine-using mothers will be related to less optimal neurobehavioral development over the first month for cocaine-exposed infants.

CHAPTER II

METHODS

Subjects

Subjects in this study were drawn from a tertiary-level teaching hospital where most patients are referred due to risk for prenatal or perinatal problems and the majority are of low socioeconomic status. The two samples included 35 cocaine-exposed infants and their mothers and 35 infant-mother dyads with no evidence of illicit drug use during pregnancy. The control group matched the cocaine-exposed group one-to-one on the following variables: maternal race, maternal tobacco use, primi- or multiparity, size for gestation, and type of delivery. Matching on race was included to control for the higher incidence of hypertensive disease among blacks. First pregnancies are generally considered higher risk than subsequent pregnancies, therefore mothers were matched on parity. Consent was usually not obtained from mothers who delivered infants by cesarean section until several days following delivery, therefore, type of delivery was included as a

matching variable in order to control for infant age at testing. Field and Widmayer (1980) found no differences in BNBAS performance between infants delivered by cesarean section and those born by spontaneous vaginal delivery. Preliminary review of the medical records of 100 consecutively born neonates indicated that the rate of admission of alcohol use during pregnancy was so low that it could not adequately be used as a matching variable; however, known alcoholics were excluded.

The cocaine-exposed group included a) infants and/or mothers who for physician-determined clinical reasons had their urine tested and were found positive for cocaine metabolites; and b) any infants whose mothers admitted to health personnel that they used cocaine at any time during their pregnancy. Control subjects had no history of cocaine use during pregnancy. Previous anonymous prevalence studies in the Well-Baby Nursery at our institution have found that only 2% of infants whose mothers did not admit cocaine use tested positive for cocaine metabolites at delivery.

All infants participating in this study were admitted to the Well-Born Nursery following delivery. All were born at a gestational age of at least 35 weeks to women at least 17 years of age who had no medical

problems adverse to pregnancy or conditions that would have made it difficult for a mother to provide informed consent. Medical reasons for exclusion from the study included conditions such as maternal diabetes, seizure disorders, epilepsy or high blood pressure requiring medication, maternal mental retardation, or maternal deafness.

Measures

Brazelton Neonatal Behavioral Assessment Scale

The Brazelton Neonatal Behavioral Assessment Scale, (BNBAS; Brazelton, 1984) was designed to supplement standard neurological examinations by providing information about the newborn infant's individual strengths and weaknesses. The BNBAS is the most well-researched and widely used neonatal assessment and has been used in previous research on cocaine-exposed infants (Chasnoff et al., 1985; Chasnoff, Griffith et al., 1989).

The BNBAS is not intended as an assessment of the infant as an isolated individual but rather seeks to assess the infant's responses to a dynamic interactional process. In fact, many of the behavioral items simulate common caregiver activities such as cuddling, consoling, and providing visual and auditory

stimulation through face-to-face interaction. The BNBAS was originally conceived as a clinical test for measuring individual neonatal behavior, but it has been used in many studies on newborn infants and certification is recommended for use in research (Brazelton 1984).

The scale includes standard tests of newborn reflexes and motoric capabilities, but it also assesses such capabilities as the ability to maintain state, to control motor and autonomic responses, and the capacity to respond to, shut out, and defend against stressful, aversive stimuli. Also of interest is the assessment of the use of and need for animate and inanimate visual and auditory information from the environment to arouse and alert the infant and help maintain interaction.

The BNBAS evaluates 20 elicited reflexes on a 4-point scale, and scores responses to 27 behavioral test items on a 9-point scale. The BNBAS does not provide one summary score. Therefore, to reduce the data for statistical analysis, individual scores are commonly grouped into the six behavioral clusters established by Lester, Als, and Brazelton (1978): habituation, orientation, motor performance, range of state, regulation of state, autonomic regulation. Also the total number of abnormal reflexes is recorded.

The 1984 version of the BNBAS which was used in this study also includes nine optional supplementary items which were designed to assess the fragile infant's ability to take in, cope with, and utilize environmental stimuli. They measure the physiological "cost" to the infant necessary to achieve and maintain an alert state.

Using the Lester cluster system, an infant who fails to reach an awake and alert state does not receive an orientation cluster score. In other words, that item would be scored as missing data in any statistical analysis. In addition, if an infant does not maintain an awake and alert state long enough to complete all six orientation items (e.g., animate and inanimate - visual, auditory, and visual/auditory items), then the cluster score is derived by dividing the sum of the item scores by the number of items completed.

In this study, infants who fail to achieve an alert state will receive an orientation cluster score of zero. If an infant does not maintain an alert state long enough to complete all of the individual orientation items, then the cluster score will be calculated by dividing the sum of the completed item scores by the total number of possible items. This change in scoring will prevent the occurrence of two

infants receiving the same orientation cluster score, when in fact, one infant was able to maintain an alert state for a longer period of time. This scoring method provides a better picture of actual performance. For example, if a greater number of cocaine-exposed infants fail to reach or maintain an alert state during the examination then that difficulty will be reflected in the group average.

Habituation items on the BNBAS can only be administered if the infant is in a sleep state at the beginning of the examination. This cluster is frequently excluded from analyses because a large proportion of the infants are awake and thus not eligible to be assessed.

Horowitz and Linn (1984) have pointed out that the BNBAS poses a challenge to the use of standard psychometric criteria for acceptance of an assessment tool. Most studies have reported low to moderate day-to-day test-retest reliability (.20-.78) for BNBAS items, as well as summary scores (Horowitz et al, 1977; Kaye, 1978; Lancioni, Horowitz, & Sullivan, 1980; Sameroff, 1978). Some researchers argue that the Pearson r , which reflects the relative position of an individual's score within a group on two occasions, is not the most direct way to measure whether an individual performs similarly twice on the same

assessment. In a sample of 60 infants, Horowitz and Brazelton (1973) calculated reliability by totaling the number of agreements and dividing this by the number of agreements plus disagreements. A score that was the same or differed by 1 point on the 9-point scale was considered an agreement. Using this method reliabilities were in the range of .23-.85 from 3 days to one month.

Many infancy researchers argue that it is necessary to consider the items or clusters in terms of the behavioral processes that are being measured. We should expect clusters that are less subject to environmental influences to be more stable, while behavioral clusters such as orientation should be more dependent on the changing environment. The basic issue is that the first month of life is a period of rapid growth. The pattern of change an infant exhibits reflects his or her ability to reorganize after the stress of labor and delivery and to respond to early environmental stimulation and caregiver efforts at interaction. Stability in behavior might actually reflect poor adaptation.

For the BNBAS, relative changes in performance are important because they measure the infants adaptation to the postnatal environment. Brazelton (1984) believes that change is the norm for infancy and that

if we hold a transactional view of development (Sameroff & Chandler, 1975) we should not expect stability. Using the BNBAS researchers have attempted to measure patterns of behavioral change over the first month of life. By testing at three times in the first month and calculating time-related and rank-related differences in the BNBAS cluster scores (Lester, 1983), several studies have been able to predict performance on later tests. Lester (1984) predicted 18 month Bayley (BSID) MDI and PDI scores, Nugent, Greene, and Brazelton (1984) found change scores predicted 3-year Stanford-Binet IQ scores, and Sepkowski, Hoffman, and Brazelton (1986) predicted 5-year McCarthy scores.

In this study it was necessary to travel in order to retest infants and mothers. Due to cost and time it was not possible to assess each infant at three different times during the first month of life. For this reason Lester's (1983) recovery curves could not be calculated. However information about infant adaptation and recovery was investigated by calculating change scores between the two testing times. Subtracting cluster scores at birth from those at one month provided information about infants' improvement or regression during the first month of life.

Beck Depression Inventory

The Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) continues to be considered the best self-report measure of general depression available for assessing the intensity of depression (Rehm, 1981). The abbreviated 13-item form which will be used in this study has been found to correlate .96 with the original (Beck, Steer, & Garbin, 1988). This short version is more appropriate for use with pregnant or recently delivered women because it excludes questions related to issues such as weight gain and frequency of sex which are confounded in this population. Burns, Melamed, Burns, Chasnoff, & Hatcher (1985) found higher scores on the Beck Depression Inventory (BDI) in a group of chemically-dependent pregnant women.

Procedures

Medical charts of all admissions to the Well-Born Nursery were reviewed daily by one of four undergraduate research assistants. During the course of the eleven month study, 78 cocaine-exposed infants were identified. Four were not eligible due to maternal retardation, maternal seizure disorder, and gestational age < 35 weeks. Thirteen were discharged

before consent could be requested. This is not uncommon in the hospital where this study was conducted. Infants are discharged on average at about 24 hours after birth. Since records were reviewed each morning, there were often only a few hours during which all infant-mother dyads identified that day could be contacted, enrolled and assessed.

Of the 61 cocaine-using mothers who were asked to participate 42 accepted (68%), compared to a 70% acceptance rate for control mothers. At the outset of this study it was not expected that the acceptance rate for cocaine-using mothers would be this high. It is important to remember that all of the cocaine-using women were in the process of being investigated by the Department of Health and Rehabilitative Services at the time consent was requested. The fact that such a high percentage of women consented to participate in a study where their only tangible compensation was one box of diapers, suggests that these women were concerned about the effect of their drug use on their infant. Eight infants were dropped from the study, six due to maternal disclosure of status and two due to medical staff disclosure. One cocaine-exposed mother-infant dyad could not be matched (a black, smoker, with no children, who vaginally delivered a large for gestational age infant).

The female principal investigator carried out all testing of mothers and infants. She was provided only with the mother's name, infant's sex, date, type and time of birth, and estimated time of discharge from the hospital for each subject. The mother was specifically told that the investigator was blind to her substance use history and needed to remain that way throughout the study. The BNBAS was administered in the Well-Baby Nursery when the infant was approximately midway between feedings. The principal investigator was certified in the administration and scoring of the BNBAS and had extensive prior experience in its use.

Subsequent to the initial testing, mothers were contacted by letter and then called by a research assistant to schedule follow-up. Twenty-two of the 36 cocaine-exposed infants were brought back for follow-up (61%). Two of these infants were brought by their foster parents, therefore maternal depressive levels could not be assessed. One mother no longer wanted to participate, five women made appointments and then failed to show up and the rest either could not be reached at the phone number given or would not return phone calls. Considering the difficulties in conducting research with infants (Miller, 1987) and the difficulties involved in research with low socioeconomic level, rural, scattered populations, it

is remarkable that 61% of cocaine-exposed infants in this study could be retested at one month of age.

Subjects lived within an 80-mile radius of the hospital, therefore, it was not possible to conduct all follow-up testing at the same location. In order to avoid wide variations in home environments and to provide a non-threatening location for mothers, half of whom were under child abuse investigation, subjects were tested at restaurants near the location of the family's home. Assessments were conducted during the mid-morning or mid-afternoon slow periods which resulted in distractions and noise levels remarkably similar to the hospital nursery.

CHAPTER III

RESULTS

Table 1 presents the proportions for each of the matching variables. By virtue of the one-to-one matching procedure, the numbers are equal in each group. As the table shows, the subjects were primarily multiparous, black smokers, who vaginally delivered average size for gestational age infants. Descriptive characteristics of the mothers and infants are found in Table 2. Cocaine-exposed infants had significantly shorter gestations and lower birthweights than did non-exposed infants. The infants did not differ on Apgar scores, head circumference, length, ponderal index, or age at the time of the first BNBAS exam. There was no difference in maternal age; however, cocaine-using women had significantly fewer prenatal visits than did the non-cocaine-using women.

Review of information contained in the clinical medical record indicated that based on maternal self-report and/or a urine toxicology screen positive for cocaine metabolites, 80% of the infants in this study were exposed to at least some cocaine beyond the first

trimester. Seventeen of the 31 mothers and/or infants who were tested for cocaine metabolites in their urine had positive results (55%). Eleven of these seventeen (65%), returned for one month follow-up. In describing their cocaine use, 77% of the women specifically used the term "crack". In addition, 23% of the control women and 60% of the cocaine-using women reported alcohol use during pregnancy. The control group admitted no use of marijuana while 26% of the cocaine group admitted use during pregnancy.

Analysis of variance between exposure status and the BNBAS clusters (Table 3) from the first assessment revealed that there were no significant differences between the cocaine-exposed and non-exposed infants on any of the BNBAS clusters when tested shortly after delivery. There were also no significant differences between the groups on the BNBAS supplementary items. Tables 4 and 5 present the means and standard deviations for data collected in the hospital following delivery.

Multivariate analysis of variance (MANOVA) was also used in order to utilize the information about the relationships (i.e., correlations) among the dependent variables. MANOVA holds the probability of a Type I error at alpha for all of the comparisons. Spearman's Rank Correlation Coefficients for the BNBAS clusters

from the assessment in the hospital revealed that the new orientation cluster was correlated with motor performance ($r = 0.35$, $p < .01$), and state regulation ($r = 0.30$, $p < .05$). In addition, motor performance was correlated with the number of abnormal reflexes ($r = -0.39$, $p < .001$). MANOVA indicated there was no overall effect of exposure status on BNBAS clusters. Table 6 presents the intercorrelations between the BNBAS supplementary items from the first BNBAS. It was not always possible to choose an appropriate score for each infant on each supplementary item. MANOVA found no overall effect of exposure status on infant scores on the nine supplementary items.

There was, however, a significant difference in maternal levels of self-reported depressive symptoms. Cocaine-using women scored significantly higher on the Beck Depression Inventory (BDI) than did women with no evidence of cocaine use (Table 4). The average in-hospital BDI score for cocaine-using women who returned for one month follow-up was 4.1 with a standard deviation of 4.1. Cocaine-using women who failed to return for follow-up had an average score of 6.6 with a standard deviation of 4.9. Despite the apparent difference in these scores, analysis on this sample of 20 cocaine-using women did not indicate that there was

differential drop-out based on the initial level of depression reported in the hospital.

Table 7 presents the means and standard deviations for the follow-up data. Cluster scores on the BNBAS at one month for this study were similar (within one-point on a nine-point scale) to those reported by Coles, Smith, Lancaster, and Falek (1987) with the exception of orientation and the number of abnormal reflexes. Their sample was similar to the sample used in this study. Women delivering at their hospital had high-risk pregnancies and were from a predominately low socioeconomic background. The infants in their study exhibited better orientation and more abnormal reflexes. The home environment in which they were tested is likely to have been more optimal for achieving a quiet-alert state than the restaurant testing location used in this study. However, it is not clear why their infants exhibited more abnormal reflexes.

MANCOVAs on the one month follow-up data revealed no significant difference between the two groups of infants, when adjusted for mother's initial score on the Beck Depression Inventory. At this testing time new orientation was correlated with motor performance ($r=.36$, $p<.01$) and motor performance was correlated with the number of abnormal reflexes ($r=-.32$, $p<.01$).

In addition, the difference in maternal depressive symptomatology found at the time of delivery was no longer apparent at one month. In fact, the means were in the opposite direction.

The nine supplementary items from the one month BNBAS were not examined due to missing data and small sample size. An ANCOVA and a MANCOVA on the difference scores (one month data - birth data) found no effect of drug exposure status on the change in infant neurobehavior or maternal depressive symptomatology over the first month (Table 8).

Table 1.
NUMBER AND PERCENTAGE OF SUBJECTS IN EACH MATCHING
VARIABLE CATEGORY

PRIMIPAROUS	9	(26%)
MULTIPAROUS	26	(74%)
BLACK	23	(66%)
WHITE	12	(34%)
LARGE FOR GESTATIONAL AGE	1	(3%)
AVERAGE FOR GESTATIONAL AGE	34	(97%)
NON-SMOKER	9	(26%)
SMOKER	26	(74%)
VAGINAL DELIVERY	32	(91%)
CAESAREAN DELIVERY	3	(9%)

Note. Due to one-to-one matching percentages are equal
in each sample

Table 2.

MEANS (AND STANDARD DEVIATIONS) FOR COCAINE-EXPOSED AND NON-EXPOSED GROUPS ON DESCRIPTIVE VARIABLES

	EXPOSED	NON-EXPOSED		
	n=35	n=35	t	
GESTATIONAL AGE	38.2 (1.8)	39.1 (1.5)	2.23	p<.05
BIRTHWEIGHT	2949.4 (444.8)	3181.6 (353.2)	2.42	p<.05
APGAR 1	7.8 (1.7)	7.9 (1.6)	0.07	N.S.
APGAR 5	8.9 (0.5)	8.8 (0.6)	0.67	N.S.
HEAD CIRCUM.	33.8 (1.3)	34.0 (1.3)	0.54	N.S.
LENGTH	49.5 (4.0)	49.9 (1.8)	0.44	N.S.
PONDERAL INDEX	2.5 (0.4)	2.6 (0.3)	1.18	N.S.
HOURS OLD ^a	31.7 (21.2)	32.3 ^b (9.5)	0.15	N.S.
DAYS OLD ^c	28.7 ^d (3.8)	28.0 ^d (4.6)	0.52	N.S.
MATERNAL AGE	25.4 (4.6)	23.9 (5.5)	1.25	N.S.
PRENATAL CARE	5.5 (4.8)	8.4 (4.7) ^b	2.46	p<.01

Note. N.S. = Non-significant difference between groups
^a Age at 1st BNBAS ^b n=34 ^c Age at 2nd BNBAS ^d n=20

Table 3.

LESTER'S CLUSTER SCORING SYSTEM (1984) FOR THE BRAZELTON
NEONATAL BEHAVIORAL ASSESSMENT SCALE

BNBAS CLUSTERS

HABITUATION	Visual	(flashlight)
	Auditory	(rattle)
	Auditory	(bell)
	Tactile	(pin-prick)
ORIENTATION	Inanimate visual	(red ball)
	Inanimate auditory	(rattle)
	Inanimate visual/auditory	(rattle)
	Animate visual	(face)
	Animate auditory	(voice)
	Animate visual/auditory	(face/voice)
	Alertness	
MOTOR	Tonus	
	Maturity	
	Pull-to-sit	
	Defensive response	
	Activity level	
RANGE OF STATE	Peak of excitement	
	Rapidity of build-up	
	Irritability	
	Lability of state	
STATE REGULATION	Cuddliness	
	Consolability	
	Self-quieting	
	Hand-to-mouth	
AUTONOMIC REGULATION	Tremors	
	Startles	
	Skin color	
ABNORMAL REFLEXES		

Table 4.
MEANS (AND STANDARD DEVIATIONS) FOR COCAINE-EXPOSED AND
NON-EXPOSED GROUPS AT BIRTH

	EXPOSED	NON-EXPOSED		
	n=35	n=35	F	
BECK DEPRESSION	5.2 (4.7) ^a	3.2 (2.6)	3.07	p<.05
<u>BNBAS CLUSTERS</u>				
NEW ORIENTATION	1.8 (1.5)	1.8 (1.7)	0.00	N.S.
MOTOR	4.4 (0.8)	4.6 (0.8)	1.11	N.S.
RANGE OF STATE	3.7 (0.6)	3.7 (0.6)	0.11	N.S.
STATE REGULATION	4.5 (1.4)	4.8 (1.6)	0.60	N.S.
AUTONOMIC REG.	7.2 (1.6)	7.2 (1.4)	0.00	N.S.
ABNORMAL REFLEXES	2.7 (2.0)	2.1 (2.1)	1.34	N.S.

Note. N.S. = Non-significant difference between groups

Table 5.
MEANS (AND STANDARD DEVIATIONS) FOR COCAINE-EXPOSED AND
NON-EXPOSED GROUPS AT BIRTH

	EXPOSED	NON-EXPOSED		
	n=35	n=35	F	
<u>BNBAS SUPPLEMENTARY ITEMS</u>				
QUALITY OF ALERTNESS	3.4 (2.0) ^b	3.5 (2.2) ^c	0.02	N.S.
COST OF ATTENTION	4.9 (1.3) ^c	4.8 (1.1) ^c	0.41	N.S.
EXAMINER PERSISTENCE	4.7 (1.1) ^a	5.1 (1.0) ^a	2.79	N.S.
GENERAL IRRITABILITY	4.3 (1.6) ^b	4.8 (1.7) ^c	1.09	N.S.
ROBUSTNESS & ENDURANCE	5.4 (1.3) ^c	5.7 (1.2)	1.03	N.S.
REGULATORY CAPACITY	4.9 (1.4) ^e	5.0 (1.8) ^b	0.03	N.S.
STATE REGULATION	5.6 (1.8) ^d	5.7 (1.9) ^a	0.21	N.S.
BALANCE OF MOTOR TONE	4.6 (1.8) ^d	4.8 (1.8) ^c	0.19	N.S.
REINFORCEMENT VALUE	4.4 (1.4) ^a	4.7 (1.6) ^b	0.88	N.S.

Note. N.S. = Non-significant difference between groups
^a n=34 ^b n=33 ^c n=32 ^d n=31 ^e n=29

Table 6.

INTERCORRELATIONS BETWEEN BNBAS SUPPLEMENTARY ITEMSBNBAS SUPPLEMENTARY ITEMS

	1	2	3	4	5	6	7	8	9
1) QUALITY OF ALERTNESS	--	.46 ^e	.28 [*]	.12	.41 ^e	.33 ⁺	.75 ^e	.20	.50 ^e
2) COST OF ATTENTION	.46 ^e	--	.49 ^e	.27 [*]	.54 ^e	.50 ^e	.44 ^e	.08	.47 ^e
3) EXAMINER PERSISTENCE	.28	.49 ^e	--	.24 [*]	.50 ^e	.47 ^e	.22	.19	.51 ^e
4) GENERAL IRRITABILITY	.12	.27 [*]	.24 [*]	--	.11	.08	.14	-.06	.09
5) ROBUSTNESS & ENDURANCE	.41 ^e	.54 ^e	.50 ^e	.11	--	.57 ^e	.48 ^e	.20	.47 ^e
6) REGULATORY CAPACITY	.33 ⁺	.50 ^e	.47 ^e	.08	.57 ^e	--	.47 ^e	.17	.61 ^e
7) STATE REGULATION	.75 ^e	.44 ^e	.22	.14	.48 ^e	.47 ^e	--	.29 [*]	.49 ^e
8) BALANCE OF MOTOR TONE	.20	.08	.19	-.06	.20	.17	.29 [*]	--	.26 [*]
9) REINFORCEMENT VALUE	.50 ^e	.47 ^e	.51 ^e	.09	.47 ^e	.61 ^e	.49 ^e	.26 [*]	--

Note. * $p < .05$ + $p < .01$ ^e $p < .001$

Table 7.
MEANS (AND STANDARD DEVIATIONS) FOR COCAINE-EXPOSED AND
NON-EXPOSED GROUPS AT ONE MONTH

	EXPOSED	NON-EXPOSED		
	n=20	n=20	F	
BECK DEPRESSION	2.9 (2.9) ^a	3.2 (2.3)	0.14	N.S.
<u>BNBAS CLUSTERS</u>				
NEW ORIENTATION	3.2 (1.6)	4.3 (2.5)	1.44	N.S.
MOTOR	4.9 (0.7)	5.4 (0.7)	1.42	N.S.
RANGE OF STATE	3.8 (0.5)	3.5 (0.9)	1.33	N.S.
STATE REGULATION	4.0 (1.3)	4.4 (1.7)	0.63	N.S.
AUTONOMIC REGULATION	8.6 (0.6)	8.4 (1.6)	0.22	N.S.
ABNORMAL REFLEXES	2.3 (1.9)	1.5 (1.4)	1.32	N.S.

Note. N.S. = Non-significant difference between groups
^a n=18

Table 8.
MEANS (AND STANDARD DEVIATIONS) FOR COCAINE-EXPOSED AND
NON-EXPOSED GROUPS DIFFERENCE SCORES (ONE MONTH-BIRTH)

	EXPOSED	NON-EXPOSED		
	n=20	n=20	F	
BECK DEPRESSION	-0.4 (2.2) ^a	0.1 (2.1)	0.45	N.S.
<u>BNBAS CLUSTERS</u>				
NEW ORIENTATION	0.8 (0.9)	2.0 (2.3)	0.86	N.S.
MOTOR	0.6 (1.0)	0.9 (0.8)	0.54	N.S.
RANGE OF STATE	-0.1 (0.6)	-0.3 (1.1)	0.32	N.S.
STATE REGULATION	-0.9 (1.8)	-0.4 (3.1)	0.48	N.S.
AUTONOMIC REGULATION	1.4 (1.7)	1.1 (1.9)	0.36	N.S.
ABNORMAL REFLEXES	-0.8 (2.5)	-0.6 (2.0)	0.38	N.S.

Note. N.S. = Non-significant difference between groups
^a n=18

CHAPTER IV

DISCUSSION

As documented in the introduction there are negative effects of prenatal cocaine-exposure. A decrease in birthweight has been found in almost every study published whether prospective or retrospective, and it was found in the present study as well. Many researchers have also documented a decrease in gestational age similar to that found in this study. The lower gestational ages found in this study are interesting, in that the sample was limited to infants less than 35 weeks gestational age and healthy enough to have been admitted to the Well-Born Nursery. This indicates that prenatal cocaine exposure may generally shorten the length of gestation whether or not an infant delivers preterm.

Chasnoff and colleagues have twice found neonatal differences in state organization or regulation when cocaine-exposed infants were compared to non-exposed infants. In their second study, they also found deficits in interactive ability and motor performance. However, in this study, which examined a population

expected to be at even greater risk due to less prenatal care and little or no drug treatment, we did not find neurobehavioral differences. What are the possible reasons for this discrepancy?

It may be that our sample had less heavy cocaine use than a sample of women who voluntarily sought treatment. In Chasnoff's second study however, even the infants of women who stopped using cocaine in the first trimester showed significantly worse orientation, motor and state regulation. Based on maternal self-report and/or a positive toxicology screen, 80% of the infants in this study were exposed to at least some cocaine beyond the first trimester (16 had urine screens positive for cocaine metabolites at delivery).

There is other indirect evidence that cocaine use was likely to be regular throughout pregnancy in the majority of the present drug group. In describing their cocaine use, 77% of the women in this study specifically referred to the use of crack. Crack cocaine is considered to be more quickly addictive than other forms of cocaine due to the intensity of the high produced by this method of administration (Perez-Reyes, DiGuseppi, & Ondusek, 1982).

In addition, the State of Florida mandates that all mothers of cocaine-exposed infants be investigated for child abuse. Women appear to be very aware of this

fact and it is our opinion that the majority of women who are still using in the latter stages of their pregnancy are addicted and are unable to stop regardless of the consequences. A mean difference of three prenatal visits in an already high-risk population may reflect avoidance of health personnel who are required by Florida law to play a disciplinary role in the lives of these women rather than the more traditional helping one.

In addition, the decreases in birthweight and gestational age, and the increase in maternal depressive symptoms support the argument that there was, probably, notable cocaine-use in this sample. Decreased birthweight is the most consistently reported result of prenatal cocaine exposure. An average 232 gram difference in birthweight is a clinically important difference, particularly between samples that were one-to-one matched on tobacco use. In Chasnoff's first study there was an average 204 gram difference between cocaine-exposed and drug-free infants; in the second study there was an average 440 gram difference between the groups. Furthermore, the higher levels of self-reported depressive symptoms in this sample of cocaine-using women is similar to that found in other substance abusing populations.

In their 1989 study, Chasnoff et al. reported similar levels of alcohol use in their two cocaine-exposed groups, but absolutely no alcohol use in the control group. This confounding factor may have contributed to the poorer BNBAS performance in their cocaine-exposed infants. Level of alcohol use is an important factor in this type of research since prenatal alcohol exposure has been found by some researchers to alter the neurobehavioral development of neonates. At a recent conference, Coles, Platzman, and James (1990) reported that controlling for alcohol use eliminated the neurobehavioral differences between groups of cocaine-exposed and non-exposed infants.

In our study, the groups were more closely balanced. At least 23% of the control group reported drinking during pregnancy, while 60% of the cocaine sample reported alcohol use. As a part of being reported to the child abuse authorities, cocaine-using mothers were interviewed by a social worker about their substance use history. It is possible that women who had already reported illegal drug use were less hesitant to admit alcohol use.

In this study it was not possible to verify the accuracy of self-reported alcohol use. In particular women in the control group were not specifically interviewed about their substance use. Therefore,

alcohol use may have been underreported in this group. It is unlikely, however, that the control group actually had significantly higher levels of alcohol use than the cocaine-using women, and that this imbalance obscured differences in neonatal neurobehavior between the two groups.

The issue of examiner blindness is always important in research but it becomes even more crucial when there are strong initial hypotheses concerning positive or negative impact on measured outcome. Cocaine-exposed infants are currently an extremely emotional and political issue. The media are flooded with images of severely preterm infants clinging to life-support systems in neonatal intensive care units. Medical journals have published numerous case reports and retrospective studies describing the detrimental effects that can occur due to prenatal cocaine-exposure. Researchers studying these infants are likely to have strong expectations about the potentially harmful effects that can occur from maternal use of such a potent vasoconstrictive substance during pregnancy. It is hypotheses such as these that stimulate research; however, it is important that studies be designed so that we do not falsely reject the null hypothesis.

When groups are compared on any measure that involves human judgment there is room for bias. Maintaining examiner blindness is not a simple issue. It involves complex, coordinated efforts among members of a research team. If one thinks in terms of a continuum of blindness, it is easier to acknowledge that there is a difference between simply not "knowing" the status of a subject and carefully designing procedures and controlling the environment to allow no cues as to status. As scientists we must take the utmost care in designing and conducting research, and this effort must be combined with a strict requirement that any subject for which identifying information becomes available be dropped from the study.

The BNBAS was designed to evaluate the infant's optimal interaction with the environment, an environment which is mediated through the evaluator who is trained to modify and alter the order and manner in which items are presented so as to elicit the infant's best response. While this results in a flexible assessment that most clearly describes the infant's ability to respond to a caretaker, it also allows for unintentional bias in administration and scoring.

The BNBAS evaluators in Chasnoff's studies were said to be "blinded to the infants' prenatal history", however there is no mention of how this was

accomplished. Were nametags removed from the infants' cribs? Were mothers given no feedback about their infant's performance on the assessment? Where other professionals instructed not to talk around the testers? In other publications, researchers who conducted the assessments for the neurobehavioral studies report how they use information from the BNBAS to educate each mother about the competencies and needs of her infant (Schneider, Griffith, Chasnoff, 1989). Women participating in the programs at the Perinatal Center for Chemical Dependency must be enrolled by the twelfth week of gestation. Therefore, many staff will have worked with these mothers for at least seven months by the time the BNBAS is administered in the hospital. It is of interest that in none of the studies published by Chasnoff and his colleagues has it been reported that an infant was dropped because the drug exposure status of the infant was unintentionally revealed to the examiner.

In addition, it is of concern that the data from the 1989 study were originally published without a control group. This raises the possibility that the drug and control groups were not tested concurrently. If that is the case then it is very likely that even if evaluators were not specifically aware of the identity

of an individual infant, they most likely had clues as to which group of infants was currently being tested.

Continuum of Casualty

The most important implication of the results found in this study may be to remind us that there is likely a continuum of casualty for any developmental toxin or teratogen. Even during the thalidomide tragedy, some children exposed to the drug during the critical period of 20-36 days postconception (Lenz, 1965) were born normal (Kajii, Kida, & Takahashi, 1973; Mellin & Katzenstein, 1962; Smithells, 1962). In our rush to document the likely negative effects of prenatal cocaine-exposure let us remain objective scientists. While it is important to encourage all pregnant women to stop using cocaine it is also important to provide rational information. Do we really want a woman who used cocaine prior to knowing she was pregnant to believe her child has been irreparably damaged? There is evidence that women overestimate the negative potential of information physicians provide to them about teratogens, and are more likely to abort than is warranted by the level of exposure (Koren, Bologa, Long, & Shear, 1989; Koren, Feldman, & MacLeod, 1990; Trichopoulos et al., 1987).

Our overreactions also may frighten away prospective adoptive parents for those infants who are removed from their homes. It is important that we carefully determine the entire range of consequences of prenatal cocaine exposure. We should also work to determine what beneficial effects might result from achieving abstinence at different points during pregnancy.

Future Research

There definitely needs to be more research into the effects of prenatal cocaine-exposure. While cocaine is probably not a teratogen, we have only preliminary evidence regarding its developmental toxicity. Even if future research fails to document any effects in the neonatal period, it is possible that CNS damage from the drug or from intrauterine hypoxia related to use, might manifest itself at later ages when greater demands are placed upon the child. Subtle deficits in motor or attentional abilities may compound their effect as the child develops. We need to remember Sameroff and Chandler's (1975) arguments about a Continuum of Caretaking Casualty. It may be that the caregiving environment either facilitates or inhibits the central nervous system's ability to repair itself.

It will require time and money to conduct the necessary longitudinal studies to answer the myriad of questions about these infants. The ideal study would require a large staff and several years. Women would be identified prenatally so that the amount, frequency, and most importantly, the timing of all licit or illicit drug use during pregnancy could be determined. Urine screening throughout the pregnancy would validate maternal reports of drug use. Prenatal enrollment of both cocaine-using women and matched controls would provide specific information about fetal loss, premature labor, and obstetrical complications. Measures of maternal stress, depression, and expectations for infant development could be administered and would provide information about differences in maternal functioning.

Mothers would need to be provided with as much promise of confidentiality as the law will allow. Ideally, in order to optimize participation, mothers would be provided protection from child abuse investigation as long as they remained in the study and continued to receive prenatal and postnatal medical care and developmental follow-up. If this protection could not be provided, then at least mothers should be assured that following initial identification to the authorities, data collected for purposes of research

would remain confidential. Good rapport would be absolutely essential in order to maintain high levels of participation. However, incentives would also encourage mothers to expend the effort necessary to participate. Depending on the geographical area involved in the study, help with transportation to and from all appointments might also be necessary.

Following delivery infants would need to be tested to assess direct effects of cocaine-exposure on initial functioning. Repeated assessments in the first month would investigate recovery from the effects of delivery and direct exposure to cocaine. Subsequent to neonatal neurobehavioral assessments, developmental progress could be monitored with the Bayley Scales of Infant Development.

Since there is poor prediction between standard developmental assessments and later performance on intelligence tests (Kopp & McCall, 1982), measures of attentional ability, such as, habituation-dishabituation or novelty preference could be included. It is possible that cocaine may effect the central nervous system in subtle ways that are not revealed by performance on standard developmental assessments of mental and motor functioning. Preliminary work by Chasnoff and Griffith indicates that there are no differences between cocaine-exposed and non-exposed

infants on the Bayley Scales at a two year follow-up (Chasnoff & Griffith, 1989). Attentional measures, however, show promise of tapping into the same mental processes as are later used on tests of intelligence and school achievement (O'Connor, Cohen, & Parmelee, 1984; Rose, Feldman, McCarton, & Wolfson, 1988; Rose & Wallace, 1985).

It would also be important to assess the caregiving environment with an instrument such as the Home Observation for Measurement of the Environment (HOME; Caldwell & Bradley, 1984). Measures of mother-infant interaction and infant attachment could evaluate the quality of socioemotional interaction. Using the measures discussed above, one could begin to investigate the transactional effects of infant behavior, caregiving environment, and prenatal cocaine exposure.

It is essential that we appreciate that any impairments resulting from prenatal cocaine-exposure are probably of multifactorial origin. To understand these effects, we must take care to distinguish between the primary or secondary embryopathic effects produced by the cocaine and the postnatal environmental-interactive effects. Ultimately, understanding these complex interactions will teach us about the development and recovery from damage of all infants.

APPENDIX

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

J. HILLIS MILLER HEALTH CENTER
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA 32610

You are being asked to volunteer as a participant in a research study. This form is designed to provide you with information about this study and to answer any of your questions.

1. TITLE OF RESEARCH STUDY

Relationship Between Mother's Self-Perception,
Mother's Perception of her Baby, Prenatal Factors,
and Actual Infant Behavior.

2. PROJECT DIRECTOR

Name: Nanci J. Stewart, M.S.

Telephone Number: 392-6427

3. PURPOSE OF THE RESEARCH

The purpose of this study is to find out how mothers feel about themselves and their babies, how their babies behave, and how prenatal factors such as smoking, alcohol or drug use during pregnancy may effect these things. We will ask you questions about how you feel about yourself and your baby in the hospital and then again when your baby is about a month old. At the same two times we will assess how your baby responds to things such as movement, sounds, objects, and people.

4. PROCEDURES FOR THIS RESEARCH

In the hospital, your baby will be developmentally assessed by a trained and experienced tester. The exam takes about 20-30 minutes and includes studying how your baby responds to being touched, held,

moved, and gently awakened, as well as how he or she responds to toys like a red ball, sounds like a bell, and an adult's face and voice. As you may know newborn babies often cry. If your baby cries during the exam the evaluator will slowly calm him or her down and see just how much help from an adult your baby needs to stop crying. This exam is called the Brazelton Neonatal Behavioral Assessment Scale and was named after and developed by a famous pediatrician Dr. Berry Brazelton whom you may have read about or seen on television.

Also, while you are in the hospital, you will be asked some questions about how you feel about yourself and also how you feel about your baby and how you expect him or her to behave. You will be told about how your baby did on the Brazelton exam and you may ask questions about your baby.

Three weeks after you go home you will be called so that we can set up a time and place to see you and your baby when he or she is about one month old. At this visit your baby will again be assessed with the Brazelton Scale which you may observe and you'll be asked the same questions concerning your feelings about yourself and your baby. As a way to thank you for your time and effort you will receive a box of diapers at this one month visit.

5. POTENTIAL RISKS OR DISCOMFORTS

There are no known risks to mothers or infants who take part in this study. All information will be kept confidential. The assessments include only questionnaires and examinations which are considered safe and not uncomfortable.

If you wish to discuss these or any other discomforts you may experience, you may call the Project Director listed in #2 of this form.

6. POTENTIAL BENEFITS TO YOU OR OTHERS

Many babies seem to enjoy being held and talked to during the Brazelton exam, and you may appreciate hearing about your baby's abilities. Because the birth of a child is often an emotional time for women, you may be interested in how your feelings about yourself and your baby change over the month following delivery.

7. ALTERNATIVE TREATMENT OR PROCEDURES, IF APPLICABLE

N/A

8. GENERAL CONDITIONS

I understand that I will _____/will not x receive money for my participation in this study. If I am compensated, I will receive _____
one box of diapers

I understand that I will _____/will not x be charged additional expenses for my participation in this study. If I am charged additional expenses these will consist of _____

I understand that I am free to withdraw my/my child's consent and discontinue participation in this research project at any time without this decision affecting my/my child's medical care. If you have any question regarding your rights as a subject, you may phone 392-3063.

In the event of my/my child's sustaining a physical injury which is proximately caused by this experiment, _____ professional medical care received at the J. Hillis Miller Health Center exclusive of hospital expenses will be provided me without charge. This exclusion of hospital expenses does not apply to patients at the Veterans Administration Medical Center (VAMC) who sustain physical injury during participation in VAMC- approved studies. It is understood that no form of compensation exists other than those described above.

I also understand that the University of Florida and the Veterans Administration Medical Center will protect the confidentiality of my records to the extent provided by Law. The Study Sponsor, Food and Drug Administration or either Institutional Review Board may ask to review my records, however the records will remain confidential as only a number and initial will be used.

9. SIGNATURES

I have fully explained to _____ the nature and purpose of the above-described procedure and the benefits and risks that are involved in its performance. I have answered and will answer all questions to the best of my ability. I may be contacted at telephone number _____ 392-6427.

Signature of Principal or Co-Principal
Investigator Obtaining Consent

Date

I have been fully informed of the above-described procedure with its possible benefits and risks and I have received a copy of this description. I have given permission of my/my child's participation in this study.

Signature of Patient or Subject or
Relative or Parent or Guardian (specify)

Date

Signature of Child (7 to 17 yrs. of age)

Date

Signature of Witness

Date

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BIOGRAPHICAL SKETCH

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I certify that I have read this study and that in my opinion it conforms to the acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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